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(71) Applicant: ELAN PHARMACEUTICALS [US/US]; 800 Gateway Boulevard, South San Francisco, CA 94080 (US).

(72) Inventors: VARGHESE, John; 1722 18th Avenue, San Francisco, CA 94122 (US). RYDEL, Russell, E.; 2120 Forest Avenue, Belmont, CA 94002 (US). DAPPEN, Michael, S.; 640 Topaz Street, Redwood City, CA 94061 (US). THORSETT, Eugene, D.; 571 Buena Vista, Moss Beach, CA 94038 (US).

(74) Agents: SNYDER, Joseph, R. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111 (US).

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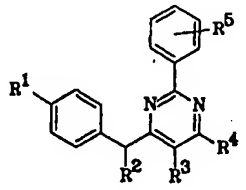

(I)

(57) Abstract

Substituted pyrimidines that have general structure (I) in which the symbol R^1 represents a C_1–C_6 alkyl, C_1–C_6 alkoxy or halogen atom; R^2 represents a phenyl group, substituted phenyl group, benzyl moiety, substituted benzyl moiety, C_3–C_7 cycloalkyl, or substituted C_3–C_7 cycloalkyl; R^3 represents a hydrogen or C_1–C_6 alkyl group; R^4 represents –H, –OH, $–N_3$ or $–NHCOCH_3$; and R^5 represents H are provided. These compounds have activity as inhibitors of phospholipase A_2, and are useful in treating disorders mediated by phospholipase A_2.

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SUBSTITUTED PYRIMIDINE COMPOSITIONS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention provides novel substituted pyrimidines. These compounds have been found to inhibit phospholipase A_2 activity, in particular $cPLA_2$ (cytosolic phospholipase A_2).

BACKGROUND OF THE INVENTION

Phospholipases A_2 (PLA_2s; EC 3.1.1.4) are enzymes that hydrolyze the 2-acyl ester bond of phosphoglycerides generating free fatty acids and lysophospholipids (for review, *see*, Kramer, RM *(1993) Advances in Second Messenger and Phosphoprotein Research* 28: 81; Glaser *et al. (1993) TiPS* 14: 92; Dennis EA *(1994) J. Biol. Chem.* 269: 13057). PLA_2s are a diverse class of enzymes with regard to function, localization, regulation, mechanism, sequence, structure, and role of divalent metal ions. A variety of polypeptide species can exhibit PLA_2 activity; for purposes of this specification, these polypeptides are considered PLA_2 isozymes.

In general, PLA_2 enzymes catalyze the hydrolysis of the fatty acid ester bond at the *sn*-2 position of membrane phospholipids to produce arachidonic acid and its metabolites. Group I, II, and III PLA_2s are extracellular enzymes of approximately 14-18 kD in humans, and are designated $sPLA_2$s, in recognition of their secretion. $sPLA_2$s are found in many extracellular fluids and have a broad substrate specificity for many types of phospholipids.

Group IV PLA_2 is a cytosolic enzyme of approximately 85 kD (based on deduced cDNA coding sequence) to 110 kD (based on SDS-PAGE of purified protein), and is designated $cPLA_2$ to indicate its cytosolic location. Unlike $sPLA_2$s, the $cPLA_2$ enzyme exhibits preferential catalysis of phospholipids which contain arachidonic acid, and is most likely the enzyme responsible for arachidonic acid release which is the rate-limiting step for subsequent eicosanoid biosynthesis of pro-inflammatory lipid mediators (prostaglandins, leukotrienes, lipoxins, and platelet-activating factor: "PAF"). $cPLA_2$ is present in the cytosol of a variety of species and cell types, including human U937 cells

(monocytes), platelets, kidney, and macrophages, among others, and is implicated in controlling arachidonic acid metabolism and eicosanoid production.

Some cells contain calcium independent phospholipase A_2/B enzyme. The phospholipase A_2/B purified enzyme is characterized by activity in the absence of calcium and having a molecular weight of 86 kD on SDS-PAGE (*see*, U.S. Patents Nos. 5,554,511 and 5,466,595).

Of particular interest in the present invention is the $cPLA_2$ enzyme. Human $cPLA_2$ has been cloned as a cDNA isolated from mRNA of a human monocytic cell line, (U.S. Patent 5,354,677 and 5,328,842; Sharp *et al. (1991) J. Biol. Chem.* 266: 14850; Clark *et al. (1991) Cell* 65: 1043) and the mRNA encodes a protein of 749 amino acids which has little detectable homology with the secreted $sPLA_2$s or any other protein in known sequence databases. The $cPLA_2$ cDNA identifies a single copy gene in the human genome, with no detectable closely related genes based on Southern blotting experiments. A suitable source of $cPLA_2$ can be obtained, if desired, by expression of a recombinant expression vector in a suitable host cell, as described in U.S. Patent 5,354,677, or by conventional biochemical purification from mammalian cells, as is known in the art.

Moreover, $cPLA_2$ contains an amino-terminal domain which binds calcium and similar divalent cations, and $cPLA_2$ binds to membrane vesicles at submicromolar concentrations of Ca^{+2} in a calcium-dependent fashion. $cPLA_2$ can translocate to membranes when activated in the presence of calcium. Presumably, $cPLA_2$ associates with membrane components *in vivo* under suitable calcium concentrations. Agents that stimulate the release of arachidonic acid (ATP, thrombin, phorbol ester, calcium ionophore) can cause increased serine phosphorylation of $cPLA_2$ which increases the enzymatic activity of $cPLA_2$ (Lin *et al. (1993) Cell* 72: 269). Phosphorylation is believed to contribute to the control of $cPLA_2$ activity *in vivo* (Lin *et al. (1992) Proc. Natl. Acad. Sci. (USA)* 89: 6147; Lin *et al. (1993) Cell* 72: 269; Qiu *et al. (1993) J. Biol. Chem.* 268: 24506; Kramer *et al. (1993) J. Biol. Chem.* 268: 26796).

The art generally recognizes the physiologic role of $cPLA_2$ to be in the mediation of inflammation via its role in arachidonic acid metabolism and lipid/lipoprotein metabolism, such as cell membrane homeostasis. Roshak *et al. (1994) J. Biol. Chem.* 269: 25999 used antisense oligonucleotides complementary to the $cPLA_2$ mRNA to inhibit prostaglandin production in LPS-induced monocytes, indicating a

potential role for $cPLA_2$ in generating inflammatory regulators in monocytes. Verity MA *(1993) Ann. N.Y. Acad. Sci.* 679:110 speculates that "abusive activation" of PLA_2 via uncontrolled Ca^{+2} influx might produce irreversible cell injury of neurons via extensive localized lipid peroxidation and subsequent membrane disintegration. U.S. Patents 5,354,677 and 5,328,842 indicates that $cPLA_2$ inhibitors are expected to be used to treat inflammatory conditions, such as psoriasis, asthma, and arthritis (*see*, col. 15), and prophesizes that such anti-inflammatory compounds can be identified as $cPLA_2$ inhibitors.

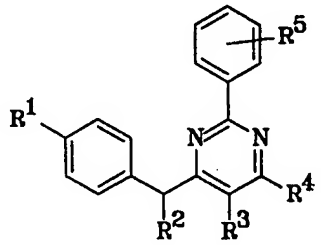
In addition to the roles mentioned above, PLA_2 activity has been implicated as a contributor to destructive cellular processes in various tissues including, but not limited to, the central nervous system. PLA_2 activity has also been reportedly involved in ischemic injury and pathological nervous system conditions.

A number of inhibitors of PLA_2 activity have been reported. Bromoenol lactone and trifluoromethyl ketones (*e.g.*, palmitoyl trifluoromethyl ketone, arachidonyl trifluoromethyl ketone) have been reported to be capable of inhibiting a Ca^{+2}-independent PLA_2 activity (*Ackermann et al. (1995) J. Biol. Chem.* 270: 445) as well as $cPLA_2$ (Street *et al. (1993) Biochemistry* 32: 5935). Several benzenesulfonamide derivatives have also been reported to be capable of inhibiting PLA_2 activity (European Patent Application 468 054; Oinuma *et al. (1991) J. Med. Chem.* 34: 2260).

In view of the role PLA_2 can play in destructive cellular processes, there is a need in the art for new compounds that are inhibitors of PLA_2. These compounds can then be used to treat or prevent PLA_2-mediated diseases. The present invention provides such new compounds, compositions and methods of treatment.

SUMMARY OF THE INVENTION

The present invention provides substituted pyrimidines which are effective inhibitors of PLA_2, more particularly $cPLA_2$. As such, the present invention provides novel substituted pyrimidines which have the general structure:



(I)

with the symbols R^1, R^2, R^3, R^4 and R^5 representing the groups provided in the detailed description below. These compounds have activity as inhibitors of phospholipase A_2, and in particular cytosolic phospholipase A_2.

In other aspects, this invention provides pharmaceutical compositions of the substituted pyrimidine compounds of formula I or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

As described in detail below, the compounds of formula I are useful in the treatment of conditions associated with PLA_2-mediated conditions, such as inflammation and Alzheimer's disease. As such, the present invention provides a method of treating $cPLA_2$-dependent diseases. In this aspect, the method comprising administering to a subject having at least one of $cPLA_2$-mediated disease with an effective amount of a compound of formula I.

The compounds and pharmaceutical compositions of compounds of formula I are also useful for *in vitro* assays for PLA_2 inhibitors. As such, in another aspect, the present invention provides a method of inhibiting PLA_2 activity *in vitro*, comprising contacting a cell having PLA_2 activity with a compound of formula I and assaying the PLA_2 activity.

In another embodiment, the present invention provides the use for the manufacture of a medicament for the treatment of inhibiting PLA_2 activity and treating $cPLA_2$-dependent diseases. These and other aspects of the present invention will be described in detail hereinbelow.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 (Panels A and B) provide synthesis schemes for the compounds of the present invention.

Figure 2 (Panels A, B, C and D) provide synthesis schemes for the compounds of the present invention.

Figure 3 (Panels A and B) provide synthesis schemes for the compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. Glossary

Abbreviations and Definitions

The term "active agent" is used herein to refer to an agent which inhibits PLA_2 activity. Active agents can be sold as commercial reagents for standardizing toxicological or pharmaceutical evaluations which employ neuron cultures or transgenic animals which exhibit neurodegenerative pathology. Some active agents will have therapeutic potential as drugs for human use such as in treating inflammation, neurodegenerative disorders or stroke patients. The active agents described herein are all substituted pyrimidines which selectively inhibit PLA_2. A selective inhibitor of PLA_2 produces a preferential inhibition of PLA_2 as compared to inhibition of other mammalian phospholipases, such that the concentration required to produce inhibition of 50% of PLA_2 catalytic activity is at least one order of magnitude lower than the concentration required to produce inhibition of 50% of the catalytic activity of phospholipases other than PLA_2. A selective inhibitor of $cPLA_2$ produces a preferential inhibition of $cPLA_2$ as compared to inhibition of other mammalian PLA_2 enzymes.

The term "PLA_2" as used herein refers to a naturally-occurring mammalian phospholipase A_2 polypeptide having enzymatic activity. These enzymes catalyze the hydrolysis of the 2-acyl ester bond of phosphoglycerides generating free fatty acids and lysophospholipids. Since the *sn*-2 position of phospholipids of mammalian cells is enriched with arachidonic acid, the precursor for eicosanoids, PLA_2 activity has important implications for the control of eicosanoid production. A paradigmatic PLA_2 can be considered to be human $cPLA_2$ substantially equivalent to that such as that described in U.S. Patent 5,354,677 and 5,328,842; Clark *et al. (1991) Cell* 65: 1043, and Sharp *et al. (1991) J. Biol. Chem.* 266: 14850, or the cognate $cPLA_2$ enzyme in a non-human

mammalian species. PLA_2 activity is present in a variety of cytosolic and extracellular PLA_2 polypeptide species. A preferred PLA_2 polypeptide of the invention is a cytosolic PLA_2, such as $cPLA_2$, and typically a calcium-activatable $cPLA_2$ which is activated (exhibits enhanced catalytic activity) by the presence of calcium ions (Ca^{+2}).

The term "$cPLA_2$-dependent disease" as used herein refers to a $cPLA_2$-mediated disease. These diseases are characterized in some instance by destructive cellular processes, membrane degradation, mitochondrial dysfunction; impaired ATP synthesis and impaired blood and oxygen delivery to tissues. These diseases include, but are not limited to, neurodegenerative diseases, cytokine-mediated conditions, conditions associated with metabolites of arachidonic acid and dysfunctions associated with inflammatory responses. (*see*, J.V. Bonventre *(1997) J. Lipid Mediators Cell Signalling*, 16: 199-208.)

The term "alkyl" refers to a cyclic, branched, or straight chain group typically containing only carbon and hydrogen, and unless otherwise mentioned, contain one to twelve carbon atoms. This term is further exemplified by groups such as methyl, ethyl, n-propyl, isobutyl, t-butyl, pentyl, pivalyl, heptyl, adamantyl, and cyclopentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, *e.g.*, halogen, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryl, arylalkyl, heteroaryl, heterocycle, amino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality.

The term "lower alkyl" refers to a cyclic, branched or straight chain monovalent alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl, and hexyl.

The term "aryl" or "Ar" refers to a monovalent unsaturated aromatic carbocyclic group having a single ring (*e.g.*, phenyl) or multiple rings either condensed rings (*e.g.*, naphthyl or anthryl), linked covalently (*e.g.*, biphenyl) or linked to a common group such as an ethylene or methylene moiety (*e.g.*, diphenylmethyl). The aromatic rings can optionally be unsubstituted or substituted with, *e.g.*, halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, arylalkyl, heteroaryl, heterocycle, amino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality. The term "aryl" is also meant to include "heteroaryl" or "HetAr"

which is an aromatic heterocycle (*e.g.* pyridine, quinoline, quinoxaline, thiophene, furan, pyrrole and the like).

The term "alkoxy" refers to a group having the structure -O-R, where R is alkyl, as described above, which may be substituted with a non-interfering substituent.

As used herein, the term "halo," "halogen atom" or "halide" refers to fluoro, bromo, chloro and iodo substituents. As used herein, the term "amino" refers to a chemical functionality $-NR^aR^b$, where R^a and R^b are independently hydrogen, alkyl, or aryl.

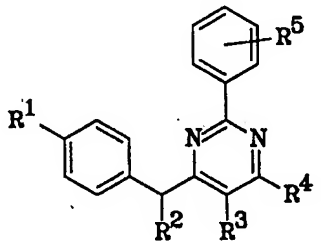
The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

Other chemistry terms herein are used according to conventional usage in the art, as exemplified by *The McGraw-Hill Dictionary of Chemical Terms (ed.* Parker, S., *1985)*, McGraw-Hill, San Francisco, incorporated herein by reference).

II. Substituted pyrimidines

A. Compounds

The present invention provides compounds which are useful for the inhibition of phospholipase A_2. In particular, the invention provides substituted pyrimidines having the formula:



(I)

In this formula, the symbol R^1 represents a C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen atom. The symbol R^2 represents a phenyl group, substituted phenyl group, benzyl moiety, substituted benzyl moiety, C_3-C_7 cycloalkyl, or substituted C_3-C_7 cycloalkyl. The symbol R^3 represents a hydrogen or C_1-C_6 alkyl group. The symbol R^4 represents —H, —OH, $—N_3$ or $—NHCOCH_3$. The symbol R^5 represents H or alkyl, preferably H.

The compounds of formula I include pharmaceutically acceptable salts, which can be salts with cations. Cations with which the compounds of this invention can

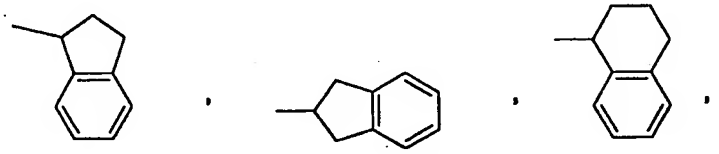
form salts include alkali metals, such as potassium and sodium or alkaline earth metals, such as calcium. Those skilled in the art will be aware of other salts which would be useful in the present invention.

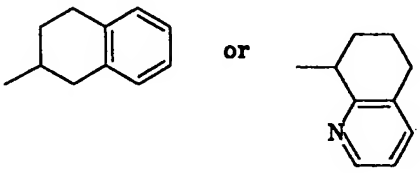
In the above definition of the compound (I) according to the present invention, the lower alkyl group defined with respect to R^1 and R^3 is a straight chain or branched alkyl group having 1 to 6 carbon atoms. Methyl, ethyl, propyl and isopropyl groups are preferred.

The lower alkoxy group is one derived from the above-mentioned lower alkyl group having 1 to 6 carbon atoms and preferable examples thereof include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy groups.

The unsubstituted cycloalkyl group defined with respect to R^2 includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and cyclododecyl groups. Preferably, the unsubstituted cycloalkyl group is a cyclopentyl group.

The substituted cycloalkyl group is a cycloalkyl group as described above which is either substituted with a lower alkyl group such as a methyl group, or a halogen atom, or can be condensed with an aromatic ring such as a benzene ring or a heterocyclic ring such as a pyridine ring at adjacent carbon atoms constituting the cyclcoalkyl group to form a condensed ring group represented by the formula:





The substituted or unsubstituted phenyl group defined with respect to R^2 is a phenyl ring which is substituted with a lower alkyl group such as a methyl, ethyl or isopropyl group, a halogen atom, or a lower alkoxy group such as a methoxy group. Still

other substituents will include nitro, amino, alkylamino, dialkylamino, carboxyl, carbamoyl, C_1-C_8 acyl, sulfonyl, thiol, alkylthio and the like, and combinations thereof. Preferably, the substituents are selected from a lower alkyl group such as a methyl or ethyl group, halogen atoms and lower alkoxy groups such as a methoxy and isopropoxy groups.

B. Methods of Preparation

The compounds of the present invention are readily prepared from commercially available starting materials via procedures and methods provided in the Examples below. Synthetic schemes which are useful for preparation of the compounds are provided as Figures 1-3.

Briefly, the pyrimidine portion of the compounds can be constructed by combining a β-keto ester with a benzamidine as illustrated in Figure 1A (using conditions described in Methods A and B, below). The resultant pyrimidine-4-ol can be further converted to 4-substituted pyrimidines (*e.g.*, 4-chloro, 4-amino, 4-azido, 4-acetamido) or the hydroxyl group can be removed using literature procedures (see Figure 1B, and Methods D-F below).

Construction of appropriate β-keto esters can be accomplished as outlined in Figure 2. For example, carboxylation of a diphenylmethane (or substituted diphenylmethane) provides a diphenylacetic acid which can be converted to a β-keto ester (see Figure 2A and procedures 4 and 5 in Section IIIB, below). The diphenylmethanes are either commercially obtained, or prepared via methods outlined in Figure 2B. Briefly, a benzaldehyde or substituted benzaldehyde can be treated with phenylmagnesium bromide (or an equivalent metallated aromatic species) to provide a benzhydrol group which can then be reduced (*e.g.*, catalytic hydrogenation) to remove the benzylic hydroxyl thereby forming a substituted diphenylmethane.

Other β-keto esters which are useful in the present invention can be prepared from substituted benzaldehydes (via substituted phenylacetic acids, see Figure 2C) and from substituted benzoic acids (via substituted benzophenones, see Figure 2D). As illustrated in Figure 2C, a substituted benzaldehyde can be reduced to the corresponding benzyl alcohol, then converted first to a phenylacetonitrile, then to a phenylacetic acid. The substituted phenylacetic acid is then converted to a β-keto ester and used as described above. Procedures 5-8, in Section IIIB below, provide

representative conditions of the processes illustrated in Figure 2C. Conversion of a substituted benzoic acid to a substituted diphenylacetic acid is illustrated in Figure 2D. Briefly, the starting acid is converted to an acid chloride which is used to acylate a second aromatic ring to provide a benzophenone. Conversion of the substituted benzophenone to a substituted diphenylacetic acid is accomplished using TosMIC to form a substituted diphenylacetonitrile which is hydrolyzed to the corresponding substituted diphenylacetic acid. Procedures 5 and 8-10 in Section IIIB below, provide representative conditions for the processes outlined in Figure 2D.

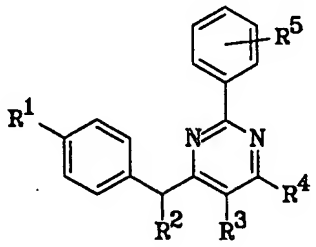
Some compounds of the present invention can be prepared by α-alkylation of pyrimidines, as illustrated in Figure 3A. According to this scheme, a pyrimidine having a benzylic group at the 6-position can be metallated (*e.g.*, using lithium diisopropylamide) and added to an alkyl halide or benzyl halide (*e.g.*, methyl iodide, cyclopentylbromide or benzyl bromide) to provide the desired targets. Method C, below, provides representative conditions.

Compounds having alkyl groups at the 5-position of the pyrimidine ring (*e.g.*, R^3 is C_1-C_6 alkyl) can be prepared by alkylating the intermediate β-keto ester as illustrated in Figure 3B. While the process is illustrated for a β-keto ester derived from a substituted diphenylacetic acid, one of skill in the art will understand that the alkylation conditions can be used with essentially any of the β-keto esters described above.

Some of the compounds of the present invention contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to include such isomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof. Conditions for the separation of enantiomers are provided in Procedure 12 in Section IIIB below. However, equivalent methods known to those of skill in the art may also be employed.

Using the methods described above, and provided in detail below, representative compounds of formula I are set forth in Table I.

TABLE I



Compound	R^1	R^2	R^3	R^4	R^5
1	isobutyl	methyl	H	—N_3	H
2	isobutyl	methyl	H	—$NHCOCH_3$	H
3	isobutyl	benzyl	H	-OH	H
4	isopropyl	benzyl	H	-OH	H
5	isobutyl	phenyl	H	-OH	H
6	isopropyl	phenyl	H	-OH	H
7	-H	4-tolyl	H	-OH	H
8	chloro	4-chlorophenyl	H	-OH	H
9	-H	cyclopentyl	H	-OH	H
10	ethyl	phenyl	H	-OH	H
11	isopropoxy	phenyl	H	-OH	H
12	methoxy	phenyl	H	-OH	H
13	ethyl	phenyl	H	-H	H
14	ethoxy	phenyl	H	-OH	H
15	propyl	phenyl	H	-OH	H
16	methoxy	4-methoxyphenyl	H	-OH	H
17	isobutyl	2,4-difluorobenzyl	H	-OH	H
18*	propyl	phenyl	H	-OH	H
19*	propyl	phenyl	H	-OH	H
20	isobutyl	2-bromophenyl	H	-OH	H
21*	isopropoxy	phenyl	H	-OH	H
22*	isopropoxy	phenyl	H	-OH	H
23	isopropyl	phenyl	CH_3	-OH	H
24	butyl	phenyl	H	-OH	H
25	ethoxy	4-ethoxyphenyl	H	-OH	H

* indicate compounds with IC_{50} < 100 nM

C. Pharmaceutical Compositions

Active agents which inhibit PLA_2 can be used to retard or reduce neurodegeneration *in vivo*. Additionally, those agents which inhibit PLA_2 activity can be used for the treatment of other conditions mediated by PLA_2, as described previously. Thus, the present invention further comprises pharmaceutical compositions incorporating one or more of the substituted pyrimidines described herein in a pharmaceutically acceptable carrier. Such pharmaceutical compositions should contain a therapeutic or prophylactic amount of at least one substituted pyrimidine. The pharmaceutically acceptable carrier can be any compatible, non-toxic substance suitable to deliver the compounds to an intended host. Sterile water, alcohol, fats, waxes, and inert solids may be used as the carrier. Pharmaceutically acceptable adjuvants, buffering agents, dispersing agents, and the like may also be incorporated into the pharmaceutical compositions. Preparation of pharmaceutical conditions incorporating active agents is well described in the medical and scientific literature. See, for example, *Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed.*, 1982, the disclosure of which is incorporated herein by reference.

The pharmaceutical compositions just described are suitable for systemic administration to the host, including both parenteral, topical, and oral administration, including intracranial administration. Thus, the present invention provides compositions for administration to a host, where the compositions comprise a pharmaceutically acceptable solution of the identified inhibitory compound in an acceptable carrier, as described above.

Compositions containing the present inhibitors (or active agents) can be administered for prophylactic and/or therapeutic treatments of neurodegenerative disease. In therapeutic application, compositions are administered to a patient already affected by the particular neurodegenerative disease, in an amount sufficient to cure or at least partially arrest the condition and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose" or "efficacious dose." Amounts effective for this use will depend upon the severity of the condition, the general state of the patient, and the route of administration, but generally range from about 1 mg to about 10g of PLA_2 inhibitor per dose, with dosages of from 10 mg to 2000 mg per patient being more commonly used. Suitable concentrations (i.e., efficacious dose) can be determined by various methods, including generating an empirical dose-response curve, predicting

potency and efficacy of a congener by using QSAR methods or molecular modeling, and other methods used in the pharmaceutical sciences. Further methods of determining an effective dose range utilize data obtained from the *in vitro* assays described herein. An effective inhibitory concentration determined in such an assay is extrapolated to estimate an effective cellular concentration *in vivo*, according to methods known in the art.

The compositions for parenteral administration will commonly comprise a solution of an active agent or a cocktail thereof dissolved in an acceptable carrier, preferably an aqueous carrier or organic solvent (*e.g.*, DMSO, solvated PEG, etc.). Since many of the active agents of the invention can be lipophilic or latentiated, it is preferable to include in the carrier a hydrophobic base (*e.g.*, polyethylene glycol, Tween 20). A variety of aqueous carriers can be used, *e.g.*, water, buffered water, 0.4% saline, 0.3% glycine and the like. These solutions are sterile and generally free of particulate matter. These compositions may be sterilized by conventional, well known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, etc. The concentration of the active agent in these formulations can vary widely, *i.e.*, from less than about 1 nM, usually at least about 0.1 mM to as much as 100 mM and will be selected primarily based on fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected. Most usually, the active agent is present at a concentration of 0.1 mM to 5 M. For example, a typical formulation for intravenous or intracranial injection comprises a sterile solution of an active agent at a concentration of 1-500 mM in Ringer's solution. The generally hydrophobic nature of some of the active agents indicates that a hydrophobic vehicle may be used, or that an aqueous vehicle comprising a detergent or other lipophilic agent (*e.g.*, Tween, NP-40, PEG); alternatively, the active agents may be administered as a suspension in an aqueous carrier, or as an emulsion.

Thus, a typical pharmaceutical composition for intramuscular injection could be made up to contain 10 mL sterile buffered water, and about 1-1000 mg of active agent. A typical composition for intravenous infusion can be made up to contain 250 mL of sterile Ringer's solution, and about 100-5000 mg of active agent. Lipophilic agents may be included in formulations. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are

described in more detail in, for example, *Remington's Pharmaceutical Science*, 15th Ed., *Mack Publishing Company, Easton, Pennsylvania (1980)*, which is incorporated herein by reference.

III. Examples

A. Assays for Determining Biological Activity

1. General

Several PLA_2 assays have previously been described. For instance, U.S. Patent 5,464,754 describes a non-radioactive, spectrophotometric, microtiter plate assay for human $cPLA_2$. In addition, Reynolds *et al. (1994) Anal. Biochem.* 217: 25 describe a convenient microtiter plate assay for $cPLA_2$. Moreover, Currie *et al. (1994) Biochem. J.* 304: 923, describe a $cPLA_2$ assay for assaying $cPLA_2$ activity from activated whole cells. This assay can be adapted for assay of related PLA_2 activity, whether from $cPLA_2$ or other PLA_2 enzymes having similar catalytic activities.

2. Inhibition of Phospholipase A_2

The PLA_2 inhibitory properties of the compounds of the present invention were evaluated using the following assays. Inhibition of release of [^{14}C]-AA from phosphatidylcholine was measured according to standard methods. Human U937 cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, penicillin, L-glutamine, and HEPES buffer. Cells were harvested and washed 3 times with extraction buffer (140 mM NaCl - 5 mM KCl - 2 mM EDTA - 25 mM Tris pH 7.4) and resuspended at 1 x 10^8 cells/mL containing 100 μM leupeptin - 50 μM pepstatin - 1 mM PMSF. Cells were placed in a N_2 cavitation bomb and put under pressure at 600 psi or maximum pressure for 20 minutes at 4°C. Cells were then released. The suspension was collected and centrifuged at 100,000g for 60 minutes at 4°C. The resulting supernatant was collected and filtered through a 0.22 μm filter. Extract was then diluted to 50% glycerol and stored at -20°C.

For the preparation of substrate, 20 nmol of phosphatidylcholine-α-1-palmitoyl-2-arachidonyl-1-[^{14}C] and 10 nmol 1,2-dioleyl-glycerol were mixed together and dried under a N_2 stream. A solution of 1 mL of 150 mM NaCl - 50 mM HEPES pH 7.5 was added to the mixture. To reconstitute liposomes, the mixture was sonicated using

a Branson 450 sonifier for 2 minutes at 50% duty cycle output level 3 on ice. After sonification, 40 μL of a 100 mg/mL BSA solution was added per mL.

The compounds were first dissolved in DMSO at 2mM and serially diluted in DMSO by a factor of five for a total of 5 concentrations. These dilutions were further dissolved 60 fold in reaction buffer (150 mM NaCl - 50 mM HEPES pH 7.5 - 1 mM $CaCl_2$ - 1 mM 2-ME) containing approximately 5% of the U937 cytosolic extract to make up the preincubation mixture which was then incubated for 20 minutes at 37°C. Vehicle control using only DMSO with no compound was also made. To 30 μL of this Extract/compound mixture was added 10 μL of substrate. The 40 μL reaction mixture was incubated for 15 minutes at 37°C, and the reaction was stopped by adding 400 μL Dole's reagent [2-propanol/heptane/0.5 M H_2SO_4 (40:10:1) 10 μg/mL stearic acid]. This was followed by the addition of 240 μL heptane and 200 μL water. 280 μL of the top heptane layer was transferred to a tube containing 60 mL silica gel with 200 μL heptane and mixed vigorously. Silica gel was then centrifuged at 1000g for 1 minute. 400 μL of liquid was transferred to scintillation vial along with 4 mL of Beckman Ready Safe scintillation cocktail and mixed. Radioactivity was determined in a Beckman scintillation counter.

B. Synthesis of Representative Compounds

1. General Methods and Procedures

All operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mmHg) with a bath temperature in the range of up to 60C; the course of the reaction was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points given are uncorrected and are obtained for materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz using the indicated solvent; conventional abbreviations used for signal shape

are: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; etc. : in addition chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), mp (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligram(s)), mmol (millimoles), eq (equivalent(s)).

The following abbreviations have the indicated meanings: Et_3N, triethylamine; Ac, acetyl; DMF, N,N-dimethylformamide; Ph, phenyl; r.t., room temperature; and TLC, thin layer chromatography.

2. Preparation of benzhydrols

4-Isopropylbenzaldehyde (1.0 equiv.) was dissolved in THF and cooled in an ice bath. Phenylmagnesium bromide (Aldrich, 3.0 M in ether, 1.1 equiv.) was added via syringe and the mixture was stirred for 30 min. The reaction was quenched by addition of satd aq NH_4Cl and the mixture was extracted with ether (2 X 100 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give a residue which was recrystallized or used crude in the next procedure.

3. Reduction to diphenylmethane

The benzhydrol was dissolved in EtOAC and 10% Pd/C was added. The mixture was hydrogenated at ca. 40 psi H_2 for 48 h. The solution was filtered through a pad of Celite to remove catalyst and evaporated in vacuo to give a residue which was purified by silica gel chromatography to give the diphenylmethane.

4. Carboxylation of diarylmethane

The diaryl methane (5 mmol) was dissolved in THF (10 mL) and cooled in an ice bath. Lithium diisopropylamide (6 mmol, 3 mL of 2M LDA in heptane) was added via syringe and the mixture was warmed to room temperature and stirred for 20 min-2 h until the deep red anion formed. The mixture was then poured onto freshly crushed dry ice (large excess) and allowed to warm to room temp. The mixture was slurried in water (50 mL) and extracted with ether (2 X 30 mL) to remove unreacted starting material. The aqueous layer is then made acidic with 1 N HCl and extracted with ether (2 X 30 mL). The combined ether extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to give the carboxylic acid.

Alternatively, the diarylmethane (5 mmol) was dissolved in THF (10 mL) and cooled in an ice bath. One drop of diisopropylamine was added, and then n-

Butyllithium (5.1 mmol, 3.2 mL of 1.6 M LDA in hexane) was added via syringe and the mixture was and stirred for 20 min-2 h until the deep red anion forms. The mixture was then poured onto freshly crushed dry ice (large excess) and allowed to warm to room temp. The mixture was slurried in water (50 mL) and extracted with ether (2 X 30 mL) to remove unreacted starting material. The aqueous layer is then made acidic with 1 N HCl and extracted with ether (2 X 30 mL). The combined ether extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to give the carboxylic acid.

5. Preparation of ß-ketoesters

The carboxylic acid was dissolved in THF (ca. 2 mL/mmol acid) and carbonyl diimidazole (1.2 equiv) was added and the mixture was stirred at room temp for 30-60 min. Meanwhile, ethyl hydrogen malonate (1.5 equiv) was dissolved in THF (ca. 3 mL/mmol above acid) and cooled to -40°C. Isopropyl magnesium chloride (2.0 M in THF, 3 equiv) was added via syringe and the mixture was allowed to warm to -20°C over 30-60 min. The resulting slightly milky solution was recooled to -40°C and the acyl imidazole solution (above) was added dropwise via cannula. The mixture was allowed to slowly warm to room temp (4 h or overnight) before addition of 1N HCl (ca. 6 equiv). After CO_2 evolution ceases, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with 1/2 satd aq $NaHCO_3$, dried, and evaporated in vacuo to yield give a residue which was purified by silica gel chromatography to yield the ß-keto ester.

6. Reduction of isobutylbenzaldehyde

Lithium aluminum hydride (586 mg, 15.4 mmol) was slurried in diethyl ether (50 mL) and cooled in an ice bath. A solution of 4-isobutylbenzaldehyde (5.00 g, 30.9 mmol) in diethyl ether (30 mL) was added dropwise over 10 min and the mixture was stirred for 30 min before successive addition of water (0.6 mL), 15% aq NaOH (0.6 mL), and water (1.8 mL). The resulting precipitate was removed via filtration and the filtrate was dried ($MgSO_4$), filtered, and evaporated in vacuo to give 4-isobutylbenzyl alcohol (4.78 g, 94%). ^1H NMR ($CDCl_3$) 7.28 (d, 2H), 7.13 (d, 2H), 4.63 (s, 2H), 2.45 (d, 2H), 1.85 (m, 1H), 0.90 (d, 6H).

7. Conversion to nitrile

4-Isobutylbenzyl alcohol (4.77 g, 29.0 mmol) was dissolved in diethyl ether and phosphorous tribromide (11.79 g, 43.1 mmol) was added and the mixture was heated to reflux for 3 h. The mixture was cooled to 0°C and carefully poured onto ice. The layers were separated and the aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated in vacuo to give the crude benzyl bromide which was used directly in the next step. ^1H NMR ($CDCl_3$) 7.31 (d, 2H), 7.12 (d, 2H), 4.49 (s, 2H), 2.46 (d, 2H), 1.85 (m, 1H), 0.89 (d, 6H).

The benzyl bromide (29 mmol) was dissolved in EtOH (105 mL) and water (45 mL) and potassium cyanide (3.40 g, 52.3 mmol) was added and the mixture was heated to reflux for 1 h. The mixture was cooled to room temp and the volatiles were removed in vacuo. The residue was diluted with water (300 mL) and the mixture was extracted with diethyl ether (2 X 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give the nitrile (4.99 g, 99%). ^1H NMR ($CDCl_3$) 7.24 (d, 2H), 7.15 (d, 2H), 3.72 (s, 2H), 2.46 (d, 2H), 1.85 (m, 1H), 0.90 (d, 6H).

8. Hydrolysis of nitrile to carboxylic acid

4-Isobutylphenylacetonitrile (4.99 g, 28.8 mmol) was dissolved in glacial acetic acid (20 mL) and 8N HCl (20 mL) was added. The mixture was heated to reflux for 48 h. The mixture was cooled to room temp and the volatiles were removed in vacuo. The residue was diluted with water (50 mL) and extracted with diethyl ether (2 X 50 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4), filtered and dried in vacuo to give the carboxylic acid (4.99 g, 90%). ^1H NMR ($CDCl_3$) 7.20-7.05 (m, 4H), 3.61 (s, 2H), 2.45 (d, 2H), 1.83 (m, 1H), 0.90 (d, 6H).

9. Preparation of substituted benzophenones

A solution of 4-isobutylbenzoic acid (5.00 g, 28.0 mmol) in CH_2Cl_2 was cooled in an ice bath and treated with oxalyl chloride (5 mL) and DMF (1 drop). The mixture was warmed to room temp and stirred 1 h. The volatiles were removed in vacuo to give the crude acid chloride which as dissolved in benzene (50 mL). Aluminum chloride (4.49 g, 33.3 mmol) was added and the mixture was heated to reflux for 3.5 h. The mixture was cooled to room temp and then poured onto ice (ca. 100 g). The mixture was extracted with EtOAc (3 X 100 mL) and the combined organic extracts were washed with 1/2 satd aqueous $NaHCO_3$ (100 mL), dried (Na_2SO_4), filtered and evaporated in

vacuo. The resulting residue was purified by silica gel chromatography (elute with 10:1 hexane/EtOAc) to give 4-isobutylbenzophenone (5.48 g, 81%). ^{1}H NMR ($CDCl_3$) 7.75 (m, 4H), 7.53 (d, 1H), 7.47 (t, 2H), 7.23 (d, 2H), 2.53 (d, 2H), 1.91 (m, 1H), 0.92 (d, 6H).

10. TosMIC reaction

A solution of tosylmethylisocyanide (2.13 g, 10.9 mmol) in DMSO (13 mL) was cooled in an ice bath and potassium tert-butoxide (3.30 g, 29.4 mmol) was added in one portion. The mixture was stirred for 5 min before addition of MeOH (0.42 mL) and 4-isobutylbenzophenone (2.00 g, 8.39 mmol). The mixture was warmed to room temp and stirred 18 h and then diluted with water (25 mL). The mixture was made acidic with 1H HCl (35 mL) and extracted with a 1:1 mixture of hexane/diethyl ether (3 X 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to give a residue which was purified by silica gel chromatography (eluted with 6:1 Hexane/EtOAc) to give the nitrile (1.62 g, 78%). ^{1}H NMR ($CDCl_3$) 7.80-7.20 (9H), 5.05 (s, 1H), 2.43 (d, 2H), 1.85 (m, 1H), 0.90 (d, 6H).

11. Alkylation of ß-keto ester

The ß-ketoester (1.00 g, 3.08 mmol) was dissolved in THF and cooled in a dry ice/iPrOH bath. Potassium tert-butoxide (518 mg, 4.62 mmol) was added, followed by iodomethane (656 mg, 4.62 mmol). The mixture was warmed to room temp and stirred 48 h before addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The EtOAc extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give the product.

12. HPLC separation of enantiomers

The enantiomers of the pyrimidines were separated via HPLC using a chiral column. A Chiracel OD-H chiral column (Diacel 588-705-50926) was used with an elution rate of 5 mL/min (elution program of 50% iPrOH/50% hexane for 25 min; then 40% iPrOH/60% hexane for 40 min). The pooled fractions were evaporated in vacuo to provide the separated isomers.

IV. METHOD OF SYNTHESIS

A. Pyrimidine preparation using sodium methoxide

The ß-keto ester (1.0 equiv) was dissolved in MeOH (5 mL) and benzamidine hydrochloride (2 equiv.) was added and the mixture was cooled in an ice bath. Sodium methoxide (0.5 M in MeOH (Aldrich), 2 equiv.) was added and the mixture was warmed to room temperature and stirred for 48 h. The mixture was diluted with 1/2 saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 X 30 mL). The combined extracts were washed with 0.2 N citric acid (30 mL) and 1/2 saturated solution of $NaHCO_3$ (30 mL), dried ($NaSO_4$), filtered and evaporated in vacuo to give a residue which was purified by silica gel chromatography to give the pyrimidine.

B. Pyrimidine preparation using potassium carbonate

The ß-keto ester (1 equiv.) was dissolved in THF (6 mL) and water (3 mL) and benzamidine hydrochloride (1.5 equiv.) and potassium carbonate (1.5 equiv.) were added and the mixture was stirred for 24 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined extracts were washed with 0.2 N citric acid (30 mL) and 1/2 satd aq $NaHCO_3$ (30 mL), dried ($NaSO_4$), filtered and evaporated in vacuo to give a residue which was purified by silica gel chromatography to give the pyrimidine.

C. α-Alkylation of Pyrimidine

The pyrimidine (1.0 equiv.) was dissolved in THF (3 mL) and cooled in a dry ice/iPrOH bath. Lithium diisopropylamide (Aldrich, 0.5 M in THF, 3.5 equiv.) was added via syringe and the mixture was stirred for 20 min before addition of neat alkyl halide (2.0 equiv.) the mixture was stirred for an additional 10 min before addition of satd aq NH_4Cl (2 mL). The mixture was allowed to warm to room temp and was diluted with water (30 mL). The mixture was extracted with EtOAc (2 X 30 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give a residue which was purified by silica gel chromatography to yield the alkylated pyrimidine.

D. Modification of 4-position with azide

The 4-hydroxy pyrimidine was slurried in $POCl_3$ and heated to reflux for 1 h. The mixture was cooled to room temp and poured onto a mixture of ice/water. The pH was adjusted to neutral with concentrated aqueous NH_4OH and the mixture was extracted with EtOAc (2 X 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to give the intermediate 4-chloropyrimidine.

The 4-chloropyrimidine was dissolved in DMF and treated with sodium cyanide and potassium carbonate. The reaction mixture was heated to 100°C. Reaction worked-up between ethyl acetate and $NaHCO_3$. The residue is purified by preparative tlc to yield desired product.

E. Modification of 4-position as acetamide

The 4-chloropyrimdine from method D was dissolved in MeOH (15 mL) in and the mixture was saturated with NH_3 gas. The mixture was heated in a sealed tube for 72 h. The volatiles were removed in vacuo and the residue was purified by silica gel chromatography (elute with 1% MeOH in CH_2Cl_2) to give the 4-aminopyrimidine.

The 4-aminopyrimidine (1.0 equiv.) was dissolved in THF and acetic anhydride (5 equiv.) and triethylamine (1.5 equiv.) were added and the mixture was stirred at room temperature. The volatiles were removed in vacuo and the residue purified by preparative silica gel TLC to give the 4-acetamidopyrimidine.

F. Modification of 4-position as a hydrogen.

The 4-chloropyrimidine (1.0 equiv) from method D was dissolved in ethyl acetate (2 mL). Potassium carbonate (1.0 equiv) was added along with 10% palladium on carbon. The mixture as hydrogenated for 48 h at 15-20 psi H_2 pressure. The mixture was filtered through a pad of diatomaceous earth and the solvent evaporated in vacuo. The residue was purified by preparative silica gel chromatography to give the pyrimidine.

EXAMPLE 1

6-(1-(4-isobutyl)phenyl)ethyl-2-phenyl-4-azido-pyrimidine, 1

Ibuprofen was transformed to a ß-keto ester using procedure 4, then converted to a pyrimidine by Method B. The pyrimidine thus obtained was converted to Compound 1 using Method D. Purification was carried out using preparative TLC to

provide the title compound as an oil. ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 1H); 7.6 (m, 2H); 7.5 (m, 1H); 7.3 (m, 2H); 3.8 (m, 1H); 3.0 (M, 1H); 1.6 (m,6H)

EXAMPLE 2

6-(1-(4-isobutyl)phenyl)ethyl-2-phenyl-4-acetamido-pyrimidine, **2**

Compound **2** was prepared from 4-chloropyrimidine by Method E. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 75-85°C, dec). ^{1}H-NMR ($CDCl_3$) δ 8.62 (s, 1H); 8.4 (m, 2H); 8.0 (s, 1H); 7.5 (m, 3H,):7.4 (d, 2H); 7.1 (d, 2H); 4.3 (m, 1H); 2.5 (d, 2H); 2.1 (s, 3H); 1.9 (m, 1H); 1.8 (d, 3H); 0.9 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 176.3; 170.3; 164.2; 158.3; 141.5; 140.7; 138.2; 131.3; 129.9; 129.1; 128.8; 128.1; 106.4; 47.9; 45.6; 30.8; 25.3; 23.0; 21.0.

EXAMPLE 3

6-(1-(4-isobutyl)phenyl-2-phenyl)ethyl-2-phenyl-pyrimidine-4-ol, **3**

Compound **3** was prepared by alkylation of the unsubstituted pyrimidine using Method C. Purification was accomplished using flash chromatography and preparative TLC to provide the title compound. ^{1}H-NMR ($CDCl_3$) δ 8.23 (m, 2H), 7.53 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.21-7.05 (7H), 6.22 (s, 1H), 407 (m, 1H), 3.66 (dd, J = 8.6, 13.5 Hz, 1H), 3.25 (dd, J = 6.5, 13.5 Hz, 1H), 2.42 (d, J = 7.2 Hz, 2H), 1.82 (m, 1H), 0.87 (d, J - 6.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 170.3, 165.4, 156.2, 140.3, 139.9, 138.9, 132.3, 131.9, 129.2, 129.0, 128.9, 128.2, 127.9, 127.8, 126.0, 111.0, 54.8, 45.0, 40.3, 30.2, 22.4.

EXAMPLE 4

6-(1-(4-isopropyl)phenyl-2-phenyl)ethyl-2-phenyl-pyrimidine-4-ol, **4**

Compound **4** was prepared similarly Compound **3**. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 152-154°C, dec). ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 2H); 7.5 (m, 3H); 7.4 (d, 2H); 7.2-7.0 (m, 7H,); 6.2 (s, 1H); 4.1 (m, 1H); 3.7 (m, 1H); 3.2 (m, 1H); 2.8 (m, 1H); 1.2 (d, 6H). ^{13}C-NMR ($CDCl_3$)

δ 170.9; 166.3; 156.9; 148.1; 140.6; 139.7; 132.9; 135.2; 129.6; 129.5; 128.9; 128.7; 128.5; 127.2; 126.7; 111.7; 55.4; 40.9; 34.3; 24.6.

EXAMPLE 5

6-(((4-isobutyl)phenyl,phenyl))methyl-2-phenyl-pyrimidine-4-ol, **5**

Compound **5** was prepared from 4-isobutylbenzaldehyde by the procedures 5-9 followed by Method A to prepare the final product. Purification was accomplished using flash chromatography to provide the title compound. ^{1}H-NMR ($CDCl_3$) δ 8.14 (m, 2H), 7.49 (m, 3H), 7.28 (m, 6H), 7.14 (m, 4H), 6.23 (s, 1H0, 5.41 (3, 1H), 2.46 (d, J = 7.2 Hz, 2H), 1.86 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.0, 165.8, 156.8, 141.4, 140.4, 138.3, 132.1, 132.0, 129.4, 129.3, 129.1, 128.9, 128.5, 127.9, 126.8, 112.4, 58.5, 44.9, 30.1, 22.3.

EXAMPLE 6

6-((4-isopropyl)phenyl,phenyl)methyl-2-phenyl-pyrimidine-4-ol, **6**

Compound **6** was prepared using synthesis described for the Compound **5** using 4-isopropylbenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 106-108°C). ^{1}H-NMR ($CDCl_3$) δ 8.15 (m, 2H); 7.45 (m, 3H); 7.3-7.1 (m, 9H); 6.3 (s, 1H); 5.4 (s, 1H); 2.9 (m, 1H); 1.2 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.0; 165.9; 156.6; 147.5; 141.5; 138.2; 132.1; 132.0; 129.5; 129.3; 128.9; 128.5; 128.0; 126.8; 126.6; 112.4; 58.5; 33.6; 23.9.

EXAMPLE 7

6-((4-methyl)phenyl,phenyl)methyl-2-phenyl-pyrimidine-4-ol, **7**

Compound **7** was prepared using the synthetic route for Compound **6** using 4-methylbenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 210-214°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3-7.2 (m, 5H); 7.1 (s, 4H); 6.2(s, 1H); 5.4 (s, 1H); 2.3 (s,3H). ^{13}C-NMR ($CDCl_3$) δ 170.9; 165.6; 156.5; 141.4; 138.2; 136.6; 132.1; 132.0; 129.4; 129.32; 129.29; 129.0; 128.5; 127.9; 126.9; 112.5; 58.4; 20.9. Mass spec (MH^+

353). Analysis for $C_{24}H_{20}N_2O$; calculated, C 81.79, H 5.72, N 7.95; found C 81.43, H 5.91, N 7.75.

EXAMPLE 8

6-(bis-(4-chloro)phenyl))methyl-2-phenyl-pyrimidine-4-ol, **8**

4,4'-Dichlorophenyl acetic acid was converted to a ß-ketoester using procedure 4. Compound **8** was then prepared using Method A. Purification was carried out using preparative TLC to provide the title compound as a solid (mp 245-246°C). ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 1H); 7.6 (m, 2H); 7.5 (m, 1H); 7.3 (m, 2H); 3.8 (m, 1H); 3.0 (m, 1H); 1.6 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ 173.3, 171.2, 165.8, 156.4, 141.3, 138.6, 132.2, 132.0, 129.0, 128.6, 127.6, 112.3. Mass spec (MH^+ 408, 409).

EXAMPLE 9

6-(1-phenyl-1-cyclohepentyl)methyl-2-phenyl-pyrimidine-4-ol, **9**

Compound **9** was prepared in manner similar to that employed for compound **8**, except that 1-cyclohepentyl-phenylacetic acid was used in place of the starting acid for compound **8**. Purification was carried out using preparative TLC to provide the title compound as a solid (mp 212.5°C). ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 1H); 7.6 (m, 2H); 7.5 (m, 1H); 7.3 (m, 2H); 3.8 (m, 1H); 3.0 (m, 1H); 1.6 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ 166.9, 161.2, 151.9, 137.8, 127.9, 127.5, 124.5, 124.1, 123.8, 123.4, 122.3, 106, 55.5, 38.8, 27.1, 27, 20.7, 20.5. Mass spec (MH^+ 331).

EXAMPLE 10

6-((2-ethyl)phenyl,phenyl)methyl-2-phenyl-pyrimidine-4-ol, **10**

Prepared as in example 6 using 4-ethylbenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 189-191°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3-7-2 (m, 9H); 6.2 (s, 1H); 5.4 (s, 1H); 2.6 (m, 2H); 1.2 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ 170.6; 165.8; 156.5; 142.9; 141.4; 138.4; 132.1; 132.0; 129.4; 129.3; 129.0; 128.5; 128.1; 128.0; 126.8; 112.4;

58.5; 28.3; 15.3. Mass spec (MH^+ 367). Analysis for $C_{25}H_{22}N_2O$; calculated, C 81.94, H 6.05, N 7.64; found C 81.74, H 6.26, N 7.46.

EXAMPLE 11

6-((4-isopropoxy)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol, **11**

Compound **11** was prepared in a manner similar to that employed in Example 6 using 4-isopropylbenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 102-108°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3 (m, 7H); 6.8 (m, 2H); 6.2 (s, 1H); 5.4 (s, 1H); 4.5 (m, 1H); 1.3 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.1; 165.9; 156.9; 156.6; 141.6; 133.0; 132.1; 132.0; 130.4; 129.4; 128.9; 128.5; 127.9; 126.8; 115.7; 112.3; 69.7; 58.0; 21.9. Mass spec (MH^+ 397). Analysis for $C_{26}H_{24}N_2O_2$; calculated, C 78.76, H 6.10, N 7.07; found C 79.89, H 6.11, N 6.81.

EXAMPLE 12

6-((4-methoxy)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol, **12**

Compound **12** was prepared in a manner similar to that employed in Example 6 using 4-methoxybenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 204-205°C). ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 2H); 7.5 (m, 3H); 7.3-7.2 (m, 7H); 6.9 (m, 2H); 6.2 (s, 1H); 5.4 (s, 1H); 3.8 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.1; 165.9; 158.5; 156.6; 141.5; 133.3; 132.1; 132.0; 130.5; 129.3; 128.9; 128.5; 127.9; 126.8; 113.4; 112.3; 58.0; 55.2. Mass spec (MH^+ 369). Analysis for $C_{22}H_{20}N_2O_2$; calculated, C 78.24, H 5.47, N 7.60; found C 78.02, H 5.57, N 7.52.

EXAMPLE 13

6-((4-ethyl)phenyl,phenyl)methyl-2-phenyl-pyrimidine, **13**

The title compound was prepared from compound **10** using Method F. Purification was accomplished using preparative TLC to provide compound **13** as an oil. ^{1}H-NMR ($CDCl_3$) δ 8.69 (d, J = 5.2 Hz, 1H), 8.42 (m, 2H), 7.45 (m, 3H), 7.34-7.24 (m,

5H), 7.16 (d, 4H), 7.01 (d, J = 5.2 Hz, 1H), 5.61 (s, 1H), 2.63 (q, J = 7.4 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.7; 164.5; 157.5; 142.9; 138.9; 137.8; 130.7; 129.4; 129.3; 128.5; 128.4; 128.1; 126.9; 119.0; 58.8; 28.3; 15.3. Mass spec (MH^+ 351).

EXAMPLE 14

6-((4-ethoxy)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol, **14**

The title compound was prepared using the procedures described in Example 6 using 4-ethoxybenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 193-196°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 1H); 7.5 (m, 3H); 7.3-7.1 (m, 7H); 6.8 (m, 2H); 6.2 (s, 1H); 5.4 (s, 1H); 4.0 (m, 2H); 1.4 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.1; 165.9; 157.9; 156.6; 141.5; 133.1; 132.1; 132.0; 130.4; 129.3; 128.9; 128.5; 127.9; 126.8; 114.4; 112.3; 63.3; 57.9 14.7. Mass spec (MH^+ 383). Analysis for $C_{25}H_{22}N_2O_2$; calculated, C 78.51, H 5.80, N 7.32; found C 77.72, H 6.00, N 6.95.

EXAMPLE 15

6-((4-n-propyl)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol, **15**

The title compound was prepared using the procedures described in Example 6 using 4-n-propylbenzaldehyde in procedure 5. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 149-154°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3-7.1 (m, 9H); 6.2 (s, 1H); 5.4 (s, 1H); 2.6 (t, 2H); 1.6 (m, 2H); 0.9 (t. 3H). ^{13}C-NMR ($CDCl_3$) δ 171.0; 165.8; 156.6; 141.43; 141.37; 138.4; 132.1; 132.0; 129.4; 129.3; 129.0; 128.6; 128.5; 127.9; 126.8; 112.4; 58.5; 37.6; 24.4; 13.8. Mass spec (MH^+ 381). Analysis for $C_{26}H_{24}N_2O$; calculated, C 82.07, H 6.36, N 7.36; found C 80.32, H 6.16, N 7.10.

EXAMPLE 16

6-(bis-(4-methoxy)phenyl)methyl-2-phenyl-pyrimidine-4-ol, **16**

The title compound was prepared using the procedures described in Example 8 using 4,4'-dimethoxyphenyl acetic acid. Purification was accomplished using

column chromatography to provide the title compound as a solid (mp 190°C, dec). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H) 7.5 (m, 3H); 7.2 (m, 3H); 6.9 (m, 4H); 6.2 (s, 1H); 5.3 (s, 1H); 3.8 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.3; 166.6; 158.5; 157.3; 133.8; 132.8; 131.7; 130.4; 128.9; 127.9; 113.9; 111.9; 57.1; 55.2. Mass spec (MH^+ 399). Analysis for $C_{25}H_{22}N_2O_3$; calculated, C 75.36, H 5.57, N 7.03; found C 74.02, H 6.06, N 7.08.

EXAMPLE 17

6-(1-(4-isobutyl)phenyl-2-(2,4-difluoro)phenyl)ethyl-2-phenyl-pyrimidine-4-ol, **17**

The title compound was prepared as in Example 3 using 2,4-difluorobenzyl bromide in Method C. Purification was accomplished using preparative TLC (2X) to provide compound **17**. ^{1}H-NMR ($CDCl_3$) δ 8.26 (m, 2H), 7.54 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.92 (dd, J = 1.9 8.5 Hz, 1H), 6.71 (m, 1H), 6.61 (m, 1H), 6.25 (s, 1H), 4.09 (m, 1H), 3.63 (dd. J = 8.5, 13.5 Hz, 1H), 3.27 (dd, J = 6.6, 13.7 Hz, 1H), 2.41 (d, J = 7.1 Hz, 2H), 1.82 (m, 1H), 0.86 (d, J = 7.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 170.0; 165.7; 156.4; 140.6; 138.5; 132.2; 132.0; 132.0; 131.9; 131.8; 129.3; 128.6; 127.9; 111.0; 52.9; 44.9; 33.1; 30.6; 22.2. Mass spec (MH^+ 445).

EXAMPLE 18

6-((4-n-propyl)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol (enantiomer 1, **18**)

Enantiomers of compound **15** were separated using procedure 11 to obtain compound **18**. Further purification was accomplished using column chromatography to provide the title compound as a solid (mp 149-154°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3-7.1 (m, 9H); 6.2 (s, 1H); 5.4 (s, 1H); 2.6 (t, 2H); 1.6 (m, 2H); 0.9 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.0; 165.8; 156.6; 141.43; 141.37; 138.4; 132.1; 132.0; 129.4; 129.3; 129.0; 128.6; 128.5; 127.9; 126.8; 112.4; 58.5; 37.6; 24.4; 13.8. Mass spec (MH^+ 381). Analysis for $C_{26}H_{24}N_2O$; calculated, C 82.07, H 6.36, N 7.36; found C 80.32, H 6.16, N 7.10.

EXAMPLE 19

6-((4-propyl)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol (enantiomer 2, **19**)

Enantiomers of compound **15** were separated using procedure 11 to obtain compound **19**. Further purification was accomplished using column chromatography to provide the title compound as a solid (mp 149-154°C). ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3-7.1 (m, 9H); 6.2 (s, 1H); 5.4 (s, 1H); 2.6 (t, 2H); 1.6 (m, 2H); 0.9 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.0; 165.8; 156.6; 141.43; 141.37; 138.4; 132.1; 132.0; 129.4; 129.3; 129.0; 128.6; 128.5; 127.9; 126.8; 112.4; 58.5; 37.6; 24.4; 13.8. Mass spec (MH^+ 381). Analysis for $C_{26}H_{24}N_2O$; calculated, C 82.07, H 6.36, N 7.36; found C 80.32, H 6.16, N 7.10.

EXAMPLE 20

6-(1-(4-isobutyl)phenyl-1-(2-bromo)phenyl)methyl-2-phenyl-pyrimidine-4-ol

Compound **20** was prepared via the methods described in Example 5 using 2-bromobenzoic acid in procedure 8. Purification was accomplished using flash chromatography to provide the title compound. ^{1}H-NMR ($CDCl_3$) δ 8.13 (m, 2H), 7.59 (m, 1H), 7.47 (m, 3H), 7.25 (m, 1H), 7.12 (m, 2H), 7.11 (s, 4H), 6.14 (s, 1H), 5.83 (s, 1H), 2.45 (d, J = 7.1 Hz, 2H), 1.85 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 169.9; 165.8; 156.5; 140.8; 140.5; 137.1; 133.2; 132.1; 132.0; 131.3; 129.4; 129.3; 128.9; 128.5; 128.0; 127.4; 125.7; 112.7; 57.5; 45.0; 30.0; 22.3. (MH^+ 473.5).

EXAMPLE 21

6-((4-isopropoxy)phenyl,phenyl)methyl-2-phenyl-pyrimidine-4-ol (enantiomer 1, **21**)

Compound **11** was separated into enantiomers using procedure 11 to obtain compound **21**. ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3 (m, 7H); 6.8 (m, 2H); 6.2 (s, 1H); 5.4 (s, 1H); 4.5 (m, 1H); 1.3 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.1; 165.9 156.9; 156.6; 141.6; 133.0; 132.1; 132.0; 130.4; 129.4; 128.9; 128.5; 127.9; 126.8; 115.7; 112.3; 69.7; 58.0; 21.9.

EXAMPLE 22

6-((4-isopropoxy)phenyl, phenyl)methyl-2-phenyl-pyrimidine-4-ol (enantiomer 2, **22**)

Compound **11** was separated into enantiomers using procedure 11 to obtain compound **22**. ^{1}H-NMR ($CDCl_3$) δ 8.1 (m, 2H); 7.5 (m, 3H); 7.3 (m, 7H); 6.8 (m, 2H); 6.2 (s, 1H); 5.4 (s, 1H); 4.5 (m, 1H); 1.3 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.1; 165.9; 156.9; 156.6; 141.6; 133.0; 132.1; 132.0; 130.4; 129.4; 128.9 128.5; 127.9; 126.8; 115.7; 112.3; 69.7; 58.0; 21.9.

EXAMPLE 23

6-((4-isopropyl)phenyl, phenyl)methyl-2-phenyl-1-methyl-pyrimidine-4-ol, **23**

The ß-keto ester used in Example **6** was alkylated with methyl iodide using procedure 10. The pyrimidine was formed by Method A. Further purification was accomplished using column chromatography to provide the title compound as a solid (mp >200°C). ^{1}H-NMR ($CDCl_3$) δ 8.15 (d, 2H); 7.3 (m, 2H); 5.6 (s, 1H); 2.9 (m, 1H); 2.25 (s, 3H); 1.23 (d, 6H). ^{13}C-NMR ($CDCl_3$) δ 4.596; 6.126; 19.435; 29.122; 49.351; 115.345; 121.905; 122.195; 122.743; 123.786; 124.468; 124.946; 125.110; 127.140; 127.822; 134.375; 137.471; 142.816; 147.746; 159.800; 160.733. Mass spec (MH^+ 395). Analysis for $C_{27}H_{26}N_2O$ + 0.8 H_2O; calculated, C 79.30, H 6.80, N 6.85; found C 79.22, H 6.67, N 6.43.

EXAMPLE 24

6-((4-butyl)phenyl,phenyl)methyl-2-phenyl-pyrimidine-4-ol, **24**

Compound **24** was prepared via the methods of Example 6 using 4-n-butyl benzaldehyde. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 118-120°C). ^{1}H-NMR ($CDCl_3$) δ 8.2 (m, 2H); 7.5 (m, 3H); 7.3 (m, 5H); 7.1 (m, 4H); 6.2 (s, 1H); 5.4 (s, 1H); 2.6 (t, 2H); 1.6 (m, 2H); 1.4 (m, 2H); 0.9 (t,3H). ^{13}C-NMR ($CDCl_3$) δ 171.0; 165.9; 156.6; 141.6; 141.4; 138.3, 132.1; 131.9; 129.4; 129.3; 128.9; 128.6; 128.5; 128.0; 126.8; 112.4; 58.5; 35.1; 33.5; 22.3; 13.8. Mass spec (MH^+ 395). Analysis for $C_{27}H_{26}N_2O$; calculated, C 82.20, H 6.64, N 7.10; found C 81.99; H 6.80, N 6.96.

EXAMPLE 25

6-(bis-(4-ethoxy)phenyl)methyl-2-phenyl-pyrimidine-4-ol, **25**

Compound **25** was prepared as in Example 8 using 4,4'-diethoxybenzoic acid in procedure 4. Purification was accomplished using column chromatography to provide the title compound as a solid (mp 167-173°C). ^{1}H-NMR ($CDCl_3$) δ 13.0 (s, 1H); 8.1 (m, 2H); 7.5 (m, 3H); 7.2 (m, 4H); 6.8 (m, 4H); 6.2 (s, 1H); 5.3 (s, 1H); 40. (m, 4H); 1.4 (t, 6H). ^{13}C-NMR ($CDCl_3$) δ 171.5; 165.8; 157.9; 156.5; 133.5; 132.1; 132.0; 130.3; 129.0; 127.9; 114.4; 112.2; 63.3; 57.2; 14.7. Mass spec (MH^+ 395). Analysis for $C_{27}H_{26}N_2O_3$; calculated, C 76.03, H 6.14, N 6.57; found C 75.79, H 6.24, N 6.48.

EXAMPLE 26

The compounds of the present invention were assayed for $cPLA_2$ activity using $cPLA_2$ enzyme from the cytosolic extraction of U937 cells (all procedures carried out on ice).

i. Cytosolic extraction of U937 cells

U937 cells were harvested and spun for five minutes at 1000g and washed at least three times in extraction buffer (140 mM NaCl, 5 mM KCl, 2 mM EDTA, 25 mM Tris, pH 7.4 solution). The cells were then suspended in buffer (1×10^8 cells/mL) and protease inhibitors were added to achieve the following concentrations: 100 μM leupeptin, 50 μM pepstatin, and 1 mM PMSF. The cells were placed in a N_2 cavitation bomb and put under pressure to 600 psi for 20 minutes in a cold room. The suspension was released and collected, then spun at 100,000g for 60 minutes at 4°C. The supernatent was collected, filtered through a 0.22 μM filter, diluted to 50% with glycerol, aliquoted and stored at -20°C.

ii. $cPLA_2$ Enzyme Assay using U937 Cytosolic Extract as Enzyme Source

a. Materials and Chemicals:

Phosphatidylcholine L-α-1-palmitoyl-2-arachidonyl-1[^{14}C] was obtained from New England Nuclear (NEC-765). 1,2-dioleyl-glycerol was obtained from Avanti

Polar Lipids (800811 in $CHCl_3$). The substrate buffer was 150 mM NaCl and 50 mM HEPES at pH 7.5. 100 mg/mL BSA (ICN 823234) was made up in water. The assay buffer was 150 mM NaCl, 50 mM HEPES at pH 7.5, 1 mM $CaCl_2$ and 1 mM 2-ME. Dole's Reagent: 2-propanol/heptane/0.5 M H_2SO_4 (40:10:1) containing 10 µg/mL stearic acid. Silica gel was 100-200 µm (70-150 mesh) (obtained from Universal Scientific Inc. 02760). Ready Safe® scintillation cocktail, 96-well deep well plates (No. 267007) and foil seals for microtiler plates (No. 538619) were all obtained from Beckman Scientific. Nunc microtiter plates were also used along with 7 mL size scintillation vials and tops.

b. Instruments:

Hamilton Microlab AT Plus was used with a 37°C incubator and a Beckman scintillation counter.

c. Hamilton At Plus Programs:

The Hamilton Microlab AT Plus was used to dilute compounds in DMSO from a 80X highest dose 1:5 dilutions for a total of 5 concentrations (80x of each dose).

The Hamilton Microlab AT Plus runs the PLA_2 assay by pipetting the DMSO dilutions into diluted extract in assay buffer (1-3 µL/well - determined by lot of extraction) into a plate for a preincubation of 20 min at 37°C. This mixture is then pipetted into the radiolabeled liposomes (substrate) starting the reaction. The program also stops the reactions, does the heptane extractions, and transfers it to the silica gel.

d. Procedure:

Preparation of substrate:

23 µL of the radiolabeled substrate was pipetted into a glass test tube and 3.1 µL of 1,2-dioleylglycerol (using a Hamilton syringe pipette) was added. Next, the solution was gently dried under an inert gas stream. The volume of the solution was increased to 1 mL using substrate buffer. The solution was then sonicated with a Branson sonifier for 2 min. at 50% max setting and 40 µL of a 100 mg/mL BSA solution was added. The solution was kept cold, on ice at 4°C.

Preparation of compounds:

To a 96-well Nunc Polysorp plate was pipetted 80 μL of DMSO into wells B1, B7, C1, C7, D1, D7. Into each of these wells was added 20 μL of a 10 mM stock solution of 6 test compounds in DMSO. The Hamilton Microlab diluted each of the test compound in DMSO (1/5) in serial dilutions, which yielded a total of five concentrations. Next, the program diluted the DMSO serial dilutions into an assay buffer containing U937 extract (5μL compound + 295 μL diluted enzyme). Then the plate was placed in 37°C for 20 min of preincubation. In the same plate, controls with assay buffer alone were added and also U937 extract diluted in the assay buffer containing 50 mM EGTA with no calcium added. During preincubation of enzyme with the test compounds, a deepwell plate was prewarmed and at 37°C. The substrate (10 μL/well) was pipetted in to this deepwell plate before the preincubation time was up.

Reaction begins:

After the preincubation time was complete, the Hamilton mixed and added 30 μL of each test compound/extract to wells containing the substrate. After the reaction started, the plate was placed back to be kept at 37°C. The plate containing the reaction mixtures was incubated at 37°C for 15 min.

Afterwards, the Hamilton added Dole's reagent to quench the reactions (400 μL). Heptane was then added (240 μL) followed by H_20 (200 μL). Next, the corresponding deepwell plate for each reaction tube was prepared by adding a slurry of 60 mg silica gel and 200 μL heptane. The Hamilton then pipetted 280 μL of the top layer (heptane phase) from the reaction plate to a silica gel plate. The silica gel plate was then sealed with foil seal tops. The plate was mixed vigorously on a microtiter plate shaker and then centrifuged at 1000g for 1 min. The Hamilton transferred 400 μL from each well to 7 mL scintillation vials. The vials were then counted after the addition of 4 mL Ready Safe Beckman scintillation cocktail. Using this method, the inhibition of $cPLA_2$ by the compounds of the instant invention were assessed.

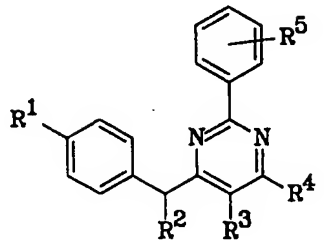
All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference for all purposes.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

5

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

wherein,

R^1 is a member selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen;

R^2 is a member selected from the group consisting of phenyl, substituted phenyl, benzyl, substituted benzyl, C_3-C_7 cycloalkyl, and substituted C_3-C_7 cycloalkyl;

R^3 is a member selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^4 is a member selected from the group consisting of —H, —OH, —N_3 and —$NHCOCH_3$;

R^5 is H; and pharmaceutically acceptable salts thereof.

2. A compound in accordance with claim 1, wherein R^1 is C_1-C_6 alkyl.

3. A compound in accordance with claim 1, wherein R^1 is C_1-C_6 alkoxy.

4. A compound in accordance with claim 1, wherein R^2 is phenyl or substituted phenyl.

5. A compound in accordance with claim 1, wherein R^2 is benzyl or substituted benzyl.

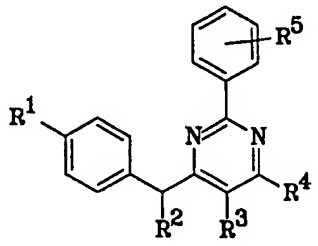
6. A compound in accordance with claim 1, wherein R^1 is C_1-C_6 alkyl, R^3 is H, R^4 is OH and R^5 is H.

7. A compound in accordance with claim **1**, wherein R^1 is C_1-C_6 alkoxy, R^3 is H, R^4 is OH and R^5 is H.

8. A compound in accordance with claim **1**, wherein R^2 is phenyl or substituted phenyl, R^3 is H, R^4 is OH and R^5 is H.

9. A compound in accordance with claim **1**, wherein R^2 is benzyl or substituted benzyl, R^3 is H, R^4 is OH and R^5 is H.

10. A pharmaceutical composition comprising a compound of formula (I)



(I)

wherein,

R^1 is a member selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen;

R^2 is a member selected from the group consisting of phenyl, substituted phenyl, benzyl, substituted benzyl, C_3-C_7 cycloalkyl, and substituted C_3-C_7 cycloalkyl;

R^3 is a member selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^4 is a member selected from the group consisting of —H, —OH, —N_3 and —$NHCOCH_3$; and

R^5 is H;

or a pharmaceutically acceptable salt thereof in unit dosage form with a pharmaceutically acceptable carrier.

11. A composition in accordance with claim **10**, wherein R^1 is C_1-C_6 alkyl.

12. A composition in accordance with claim **10**, wherein R^1 is C_1-C_6 alkoxy.

13. A composition in accordance with claim **10**, wherein R^2 is phenyl or substituted phenyl.

14. A composition in accordance with claim **10**, wherein R^2 is benzyl or substituted benzyl.

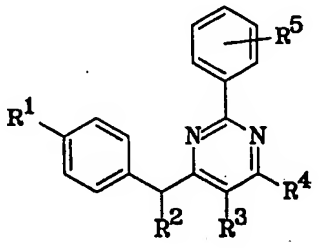
15. A composition in accordance with claim **10**, wherein R^1 is C_1-C_6 alkyl, R^3 is H, R^4 is OH and R^5 is H.

16. A composition in accordance with claim **10**, wherein R^1 is C_1-C_6 alkoxy, R^3 is H, R^4 is OH and R^5 is H.

17. A composition in accordance with claim **10**, wherein R^2 is phenyl or substituted phenyl, R^3 is H, R^4 is OH and R^5 is H.

18. A composition in accordance with claim **10**, wherein R^2 is benzyl or substituted benzyl, R^3 is H, R^4 is OH and R^5 is H.

19. A method of treating a $cPLA_2$-dependent disease, comprising administering to a subject having at least one of said diseases an effective amount of a compound of formula:



(I)

wherein,

R^1 is a member selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen;

R^2 is a member selected from the group consisting of phenyl, substituted phenyl, benzyl, substituted benzyl, C_3-C_7 cycloalkyl, and substituted C_3-C_7 cycloalkyl;

R^3 is a member selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^4 is a member selected from the group consisting of —H, —OH, —N_3 and —$NHCOCH_3$; and

R^5 is H;

or a pharmaceutically acceptable salt thereof in unit dosage form with a pharmaceutically acceptable carrier.

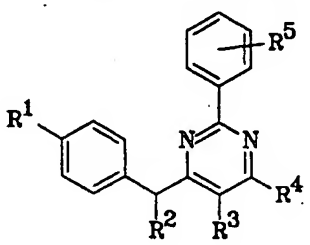
20. A method in accordance with claim **19**, wherein R^1 is C_1-C_6 alkyl, R^3 is H, R^4 is OH and R^5 is H.

21. A method in accordance with claim **19**, wherein R^1 is C_1-C_6 alkoxy, R^3 is H, R^4 is OH and R^5 is H.

22. A method in accordance with claim **19**, wherein R^2 is phenyl or substituted phenyl, R^3 is H, R^4 is OH and R^5 is H.

23. A method in accordance with claim **19**, wherein R^2 is benzyl or substituted benzyl, R^3 is H, R^4 is OH and R^5 is H.

24. A method of inhibiting PLA_2 activity *in vitro*, said method comprising contacting a cell having PLA_2 activity with a compound of formula:



(I)

wherein,

R^1 is a member selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen;

R^2 is a member selected from the group consisting of phenyl, substituted phenyl, benzyl, substituted benzyl, C_3-C_7 cycloalkyl, and substituted C_3-C_7 cycloalkyl;

R^3 is a member selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^4 is a member selected from the group consisting of —H, —OH, —N_3 and —$NHCOCH_3$; and

R^5 is H;

or a pharmaceutically acceptable salt thereof; and assaying said PLA_2 activity.

25. A method in accordance with claim 24, wherein R^1 is C_1-C_6 alkyl, R^3 is H, R^4 is OH and R^5 is H.

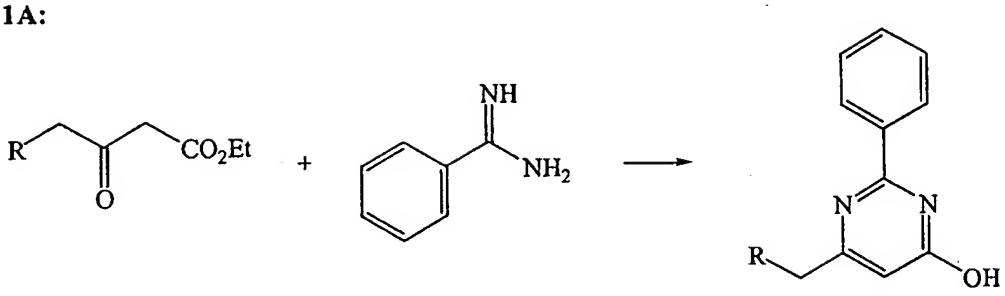
26. The use of a composition in accordance with claim 1, in the manufacture of a medicament for inhibiting PLA_2 activity or for the treatment of a $cPLA_2$-dependent disease.

27. The use of a composition in accordance with claim 26, in the manufacture of a medicament for inhibiting a $cPLA_2$-dependent disease wherein said $cPLA_2$-dependent disease is a member selected from the group consisting of a neurodegenerative disease, a cytokine-mediated condition, a condition associated with

metabolites of arachidonic acid and a dysfunction associated with an inflammatory response.

Figure 1

1A:



1B:

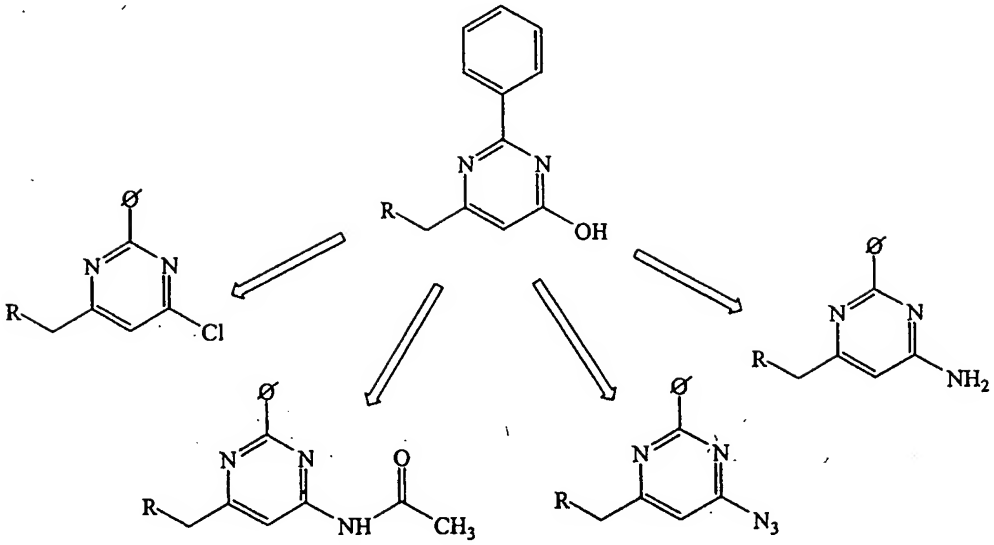
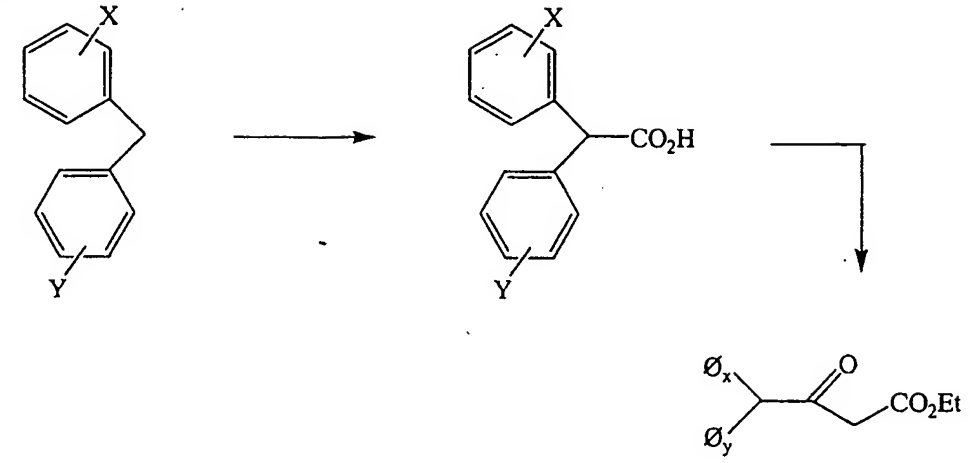


Figure 2

2A:



2B:

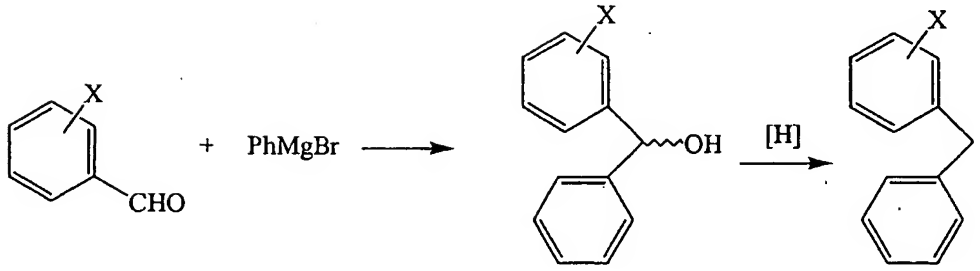


Figure 2 (continued)

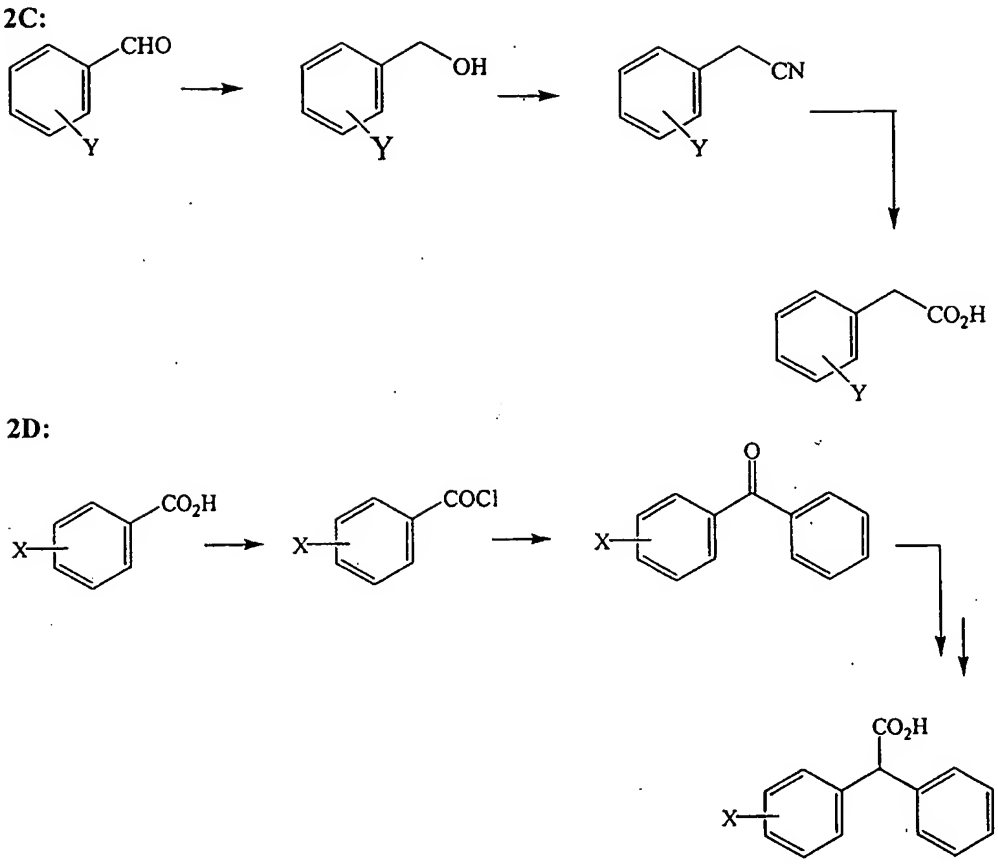


Figure 3

3A:

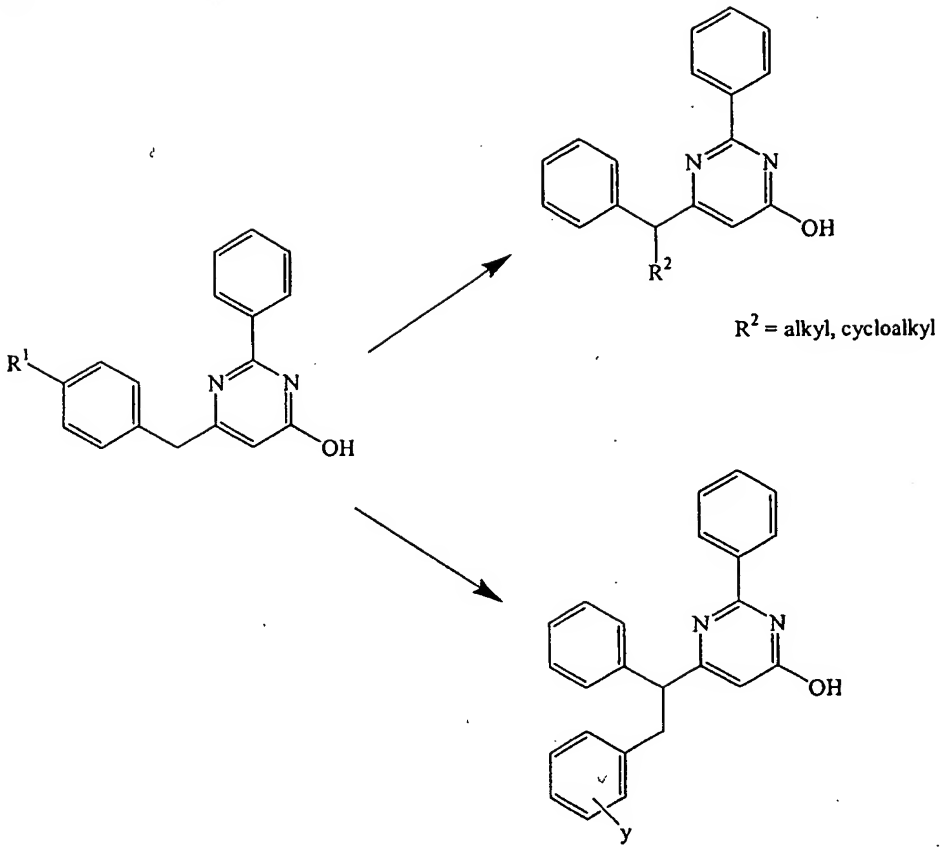
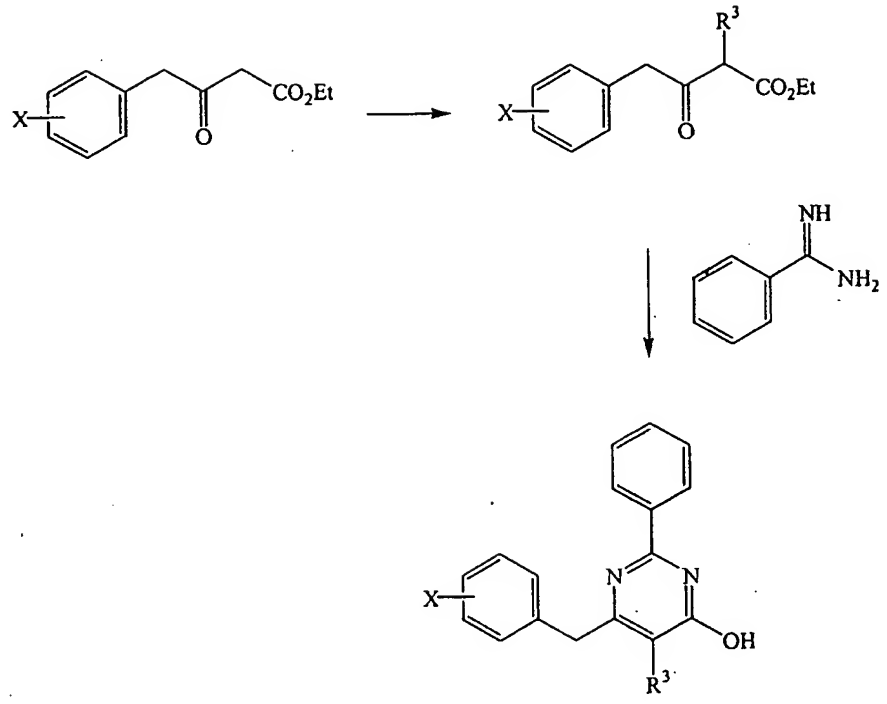


Figure 3 (continued)

3B:



INTERNATIONAL SEARCH REPORT

Inter. ..onal Application No
PCT/US 99/26550

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/36 C07D239/42 A61K31/505 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 424 317 A (CIBA-GEIGY) 24 April 1991 (1991-04-24) claims	1,10,24
A	CHEMICAL ABSTRACTS, vol. 75, no. 7, 1971 Columbus, Ohio, US; abstract no. 49022w, AROYAN,A.: "PYRIMIDINE DERIVATIVES.SUBSTITUTED 6-(4'-ALKOXYBENZYL)PYRIMIDINES." page 362; XP002132439 abstract & ARM. KHIM. ZH., vol. 24, no. 2, 1971, pages 161-6, RUSS	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2000	21/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 26550

Box I Observations where certain claim were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-23
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter... nal Application No
PCT/US 99/26550

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ZA 9008344 A	26-06-1991